9-2018

Pharmacy Newsletter : September 2018

Pharmacy Department
Aga Khan University Hospital

PHARMACY NEWSLETTER

September, 2018 Vol. 29, Issue 02

Published by
Drug & Poison Information Centre
Pharmacy Services
Aga Khan University Hospital Stadium Road, P.O. box 3500, Karachi 74800, Pakistan

Pharmacy Newsletter provides information regarding the decisions of P & TC, current concepts in drug therapy, warnings and cautions issued by various regulatory agencies, drug interactions, ADRs and matters related to drug usage.

Opinions expressed are of authors and does not necessarily represent AKUH's view/recommendations.
Publication of this newsletter has been through an endowment grant from Pharmacist group of Ontario, Canada

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Inside this Issue:

Stress Ulcer Prophylaxis

Muhammad Amir, Specialist Clinical Pharmacy

It is general practice to initiate Acid Suppressing Medications (ASM) as Stress ulcer prophylaxis (SUP) to reduce the risk of gastrointestinal bleeding (GlB), albeit researches shows that SUP is continued for longer period than required. Researches also shows that 28% of ICU patients receive inappropriate ASM and 81% are inappropriately continued on SUP upon transfer from lCU. Recently, two major concerns with respect to ASM has been raised. First, an increased risk of C. Difficile and nosocomial infection. Secondly, it is found that ASMs do not affect the rate of GI bleed with no risk factors. Sucralfate is commonly not been used as SUP due to its increased drug interaction. Proton Pump Inhibitors (PPI) and Histamine Receptor Antagonist (H2RA) are commonly used and suggested for SUP. No ASMs have been found superior to each other for this indication in terms of health outcomes (benefit or adverse) and cost.
To standardized use of ASM in Surgical ICU, guideline is established to ensure its appropriate use and discontinuation. Ranitidine is suggested as the first line therapy because of its better pharmacokinetic profile and cost minimization value. Its pharmacokinetic profile allows a dosing regimen which does not fully suppress gastric acid and may limit infection risk. Additionally, Omeprazole interaction with QT prolonging drugs is an upcoming concern also. Furthermore, interaction of Omeprazole with Clopidogrel can also be avoided. The efficacy of Clopidogrel reduced by omeprazole due to inhibition of its metabolism pathway (CYP2C19), hence it was suggested that patient prescribed with Clopidogrel should be either be on ranitidine (lV/ Oral) or pantoprazole. Details of the guideline can be found in:

http://betaportal.aku.edu/GI-Surgery/Key%20Documents/Policies,%20Procedures,%20Protocols,%20Clinical%20Practice%20Guideline/Guideline%20for%20Prophylaxis%20for%20Stress%20Ulcer.pdf

Use of Diazoxide in Hypoglycemia due to Hyperinsulinism in Neonates

Gul Ambreen, Senior Pharmacist

Diazoxide is the drug of choice for the treatment of persistent and severe hypoglycemia due to hyperinsulinism in neonates. It is a nondiuretic hypotensive and antihypoglycemic agent that is structurally related to the thiazide diuretics. Diazoxide increases blood glucose concentration by inhibiting pancreatic insulin secretion, stimulating the release of catecholamines and/or increasing the hepatic release of glucose. Diazoxide has a marked inhibitory effect on glucose induced insulin secretion. After oral administration of Diazoxide suspension in the doses of 10-15mg/kg/day in two to three divided doses with feed. Hyperglycemic effects begin within 1 hour and last approximately 8 hours in patients with normal renal function. 1 It reduces peripheral vascular resistance and blood pressure as a result of direct vasodilatory effect on smooth muscle in peripheral arterioles. Diazoxide causes sodium and water retention and decreased urinary output, which can result in expansion of plasma and extracellular fluid volume, edema and congestive cardiac failure. Concurrent administration of a diuretic (e.g. hydrochlorathiazide) is recommended. [2]

Other Possible Adverse Effects: [3]

1. Hypertrichosis
2. Neonatal jaundice

3. Gastrointestinal disturbances (nausea and vomiting).
4. Arrhythmias, tachycardia.
5. Elevated serum uric acid levels
6. Cerebral ischemia/convulsions.
7. Blood dyscrasias (neutropenia, leukopenia, and thrombocytopenia).
8. Transient cataracts with prolonged use.
9. Pulmonary hypertension
10. Dilatation of the ductus arteriosus

Contraindicated in compensatory hypertension with aortic coarctation or AV shunt.
Use with **caution** in infants with congestive heart failure and renal insufficiency and impaired carbohydrate metabolism. [3]

Special Considerations[3]

1. Is NOT a drug of choice in treatment of hypertensive emergencies in newborns.
2. Hypokalemia potentiates the hyperglycemic effect.
3. Diazoxide causes sodium retention and diuretics may need to be administered concomitantly

Drug Interactions: Concomitant administration with diuretics, anti-hypertensive, and corticosteroids potentiates hyperglycemia and hypotension. Concomitant administration with phenytoin has resulted in both failures to achieve seizure control and phenytoin toxicity [1].

Monitoring parameters:

1. Monitor glucose levels carefully.
2. Monitor blood pressure.
3. Continuous cardiorespiratory monitoring. Observe for arrhythmias.
4. Monitor fluid balance carefully.
5. Weigh daily.
6. CBC
7. Uric acid concentration (specially for long-term treatment)

Antidote: Discontinue Diazoxide; administer insulin as necessary for hyperglycemia; treat hypotension with sympathomimetic agents.

References:

1. *Diazoxide: AHFS Detalied Monogrpah. Medscape. http://www.medscape.com/druginfo/monograph?cid=med&drugid=10322&drugname=Diazoxide+IV&monotype=monograph. Accessed on 30/07/2007.*
2. *Aynsley-Green A, Hussain K, Hall J, Saudubray JM, Nihoul-Fekete C, De Lonlay-Debeney P, Brunelle F, Otonkoski T, Thornton P and Lindley KJ. Practical management of hyperinsulinism in infancy. Arch Dis Child Fetal Neonatal Ed 2000; 82: F98-F107*
3. *NeoFax Essentials 2017*

New Update: Direct Oral Anti-Coagulants (DOACs)

Kashif Hussain, Specialist Clinical Pharmacy

American College of Cardiology issued a specialist accord archive in December 2017 to help doctors on the management of bleeding in patients taking oral anticoagulants. Since normal activated partial thromboplastin time (aPTT) is not useful for monitoring new DOACs and these assays are not readily available. Recommendation includes:

1-Dabigatran is reversible with the monoclonal antibody derived antidote, Idarucizumab. The antidote is indicated for severe bleeding in patients taking Dabigatran.

2- Andexanet alfa, an antidote to factor Xa, was approved by the FDA in May 2018 with indications for patients with major bleeding while taking factor Xa inhibitors Rivaroxaban and Apixaban.

3- Prothrombin complex concentrate has been suggested as a treatment for bleeding due to DOACs other than Dabigatran.

Crossing over anticoagulation with enoxaparin or other low molecular weight heparin drugs in the perioperative period is not viewed as essential or prudent for most patients taking DOACs. The medication can essentially be halted for a time of days before the surgery.

Most patients can be restarted on their oral anticoagulant 24 hours in the wake of experiencing a medical procedure or system that conveys a generally safe of post procedure bleeding. Restarting anticoagulation following 2 to 3 days is prompted for patients at higher hazard for bleeding.

For reversal of warfarin, **vitamin K** is still considered the first-line agent, preferably to be infused by slow intravenous dosing. Prothrombin complex concentrates have also been suggested for reversal of serious bleeding associated with warfarin.

References:

1- Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. J Am Coll Cardiol. 2017 Dec 19;70(24):3042-3067.

Case Study: Use of Cholestyramine for Management Of Digoxin Toxicity

Mahreen Muzammil, Clinical Pharmacist, Pharmacy Services

A female patient came with digoxin toxicity with the levels of 2.9 ng/mL (0.5–2 ng/mL). It was suggested to add Cholestyramine 4 gram every six hourly. Digoxin level was 0.9 ng/mL on next day.

The effectiveness of Cholestyramine have been proven in many studies for toxication of digoxin. Due to Cholestyramine, the serum concentration of digoxin reduces rapidly, and its half-life decreases from 75.5 hours to 19.9 hours. All signs and symptoms of toxic reaction also subsides during the its period of therapy. Cholestyramine and a related agent, colestipol, presumably interrupt the enterohepatic recycling of digoxin to enhance elimination. These agents represent potentially useful adjunctive measures in the management of non— life-threatening digitalis intoxication. [1]

References:

1- Henderson, R. P. and C. P. Solomon (1988). "Use of cholestyramine in the treatment of digoxin intoxication." Archives of internal medicine 148(3): 745-746.

Updates : Use of Doxycycline in Children

Taniya Zaidi, Pharmacist

Tetracycline are bacteriostatic antibiotics that are used to treat infection caused by many aerobic gram-positive and gram-negative bacteria. Doxycycline is one of the most active tetracyclines and is the most often used clinically since it possesses many advantages over traditional tetracycline and minocycline. Use of tetracyclines is restricted in children under 8 years of age because of its side effect, teeth discoloration. The degree of staining appears to depend on dosage, duration of therapy, and which drug in the tetracycline class is used. However, doxycycline binds less readily to calcium than other tetracyclines, and the risk of dental staining with short courses of doxycycline is minimal. In an observational study of 53 children who received approximately two courses of doxycycline for Rocky Mountain spotted fever before they were eight years old, none developed dental staining in their permanent teeth. Updated recommendations from the American Academy of Pediatrics now permit doxycycline for ≤21 days in children of all ages. The dose of doxycycline, as per WHO expert recommendation is 5mg/kg/day in 2 divided doses.

References:

American Academy of Pediatrics. Tetracyclines. In: Red Book: 2018 Report of the Committee on Infectious Diseases, 31st ed, Kimberlin DW, Brady MT, Jackson MA, Long SS (Eds), American Academy of Pediatrics, Itasca, IL 2018. p.905.

Serotonin Syndrome – Myths & Misconceptions

Hafsah Ashfaq, Clinical Pharmacist

Serotonin syndrome (SS) is an actually life-threatening condition associated with increased serotonergic activity in the central nervous system (CNS). It is seen with therapeutic medication use, unintended interactions between drugs, and deliberate self-poisoning.

The Hunter criteria is used to diagnose the SS which focus more on the neuromuscular findings of clonus, muscle rigidity, tremor, and hyperreflexia—are more reliable for diagnosing SS.

Two common misunderstandings are responsible for the inaccurate listing of various drugs as causes of SS. First, drugs capable of producing serotonergic effects differ widely in their possibility of causing SS. Just combining 2 serotonergic drugs does not certainly increase the risk for SS. There are different serotonin receptors, and only some of them appear to be involved in the etiology of SS. Second, very few drugs (mainly the monoamine oxidase inhibitors) are capable of producing severe SS, while a much greater number of drugs can cause mild to moderate SS.

The prevalence of serotonin syndrome is increasing with the expanded use of serotonergic agents and, specifically, with polypharmacy.

Treatment includes removal of the causative agents and may also include the use of serotonin antagonists (i.e., cyproheptadine).

Immediate symptomatic management like hypertension, tachycardia, hyperthermia, and respiratory distress. Usually symptoms resolves within 24 hours of discontinuation of causative drugs. Benzodiazepines, such as diazepam or lorazepam, usually used to decrease agitation, myoclonus, and muscle rigidity.

Prevention of Serotonin Toxicity

Complete medication history to be taken in order to identify patients at risk. Prescribers should reconsider the use of two or more serotonergic medications and/or consider switching to less-serotonergic alternatives, if appropriate.

Pharmacists should monitor medication regimens for interactions between serotonergic agents and counsel patients. Educating patients at risk for potential adverse effects from serotonergic agents (e.g., muscle spasms, confusion, sweating, shaking, shivering) should be an essential part of counseling.

COMBINATIONS THAT MAY RESULT IN SEROTONIN SYNDROME

All SSRIs in combination	Clomipramine And Trazodone
Venlafaxine And Lithuim	Clomipramine And Moclobemide
Venlafaxine And Moclobemide	Dextromethorphan And Paroxetine
Venlafaxine And Fluoxetine	Dextromethorphan And Moclobemide
Venlafaxine And Mirtazapine	Linezolid And Citalopram
Fluoxetine And Sertraline	SSRIs And St. John's Wort
Fluoxetine And Tramadol	SSRIs and MAOI
Trazodone And Buspirone	Meperidine And MAOI
Clomipramine And MAOI	

SSRIs : selective serotonin reuptake inhibitors, MAOI : Monoamino oxidase inhibitors

References:

- *Iqbal MM, Basil MJ, Kaplan J, Iqbal MT. Overview of serotonin syndrome. Ann Clin Psychiatr. 2012;24:310-318.*
- *Sternbach H. The serotonin syndrome. Am J Psychiatry. 1991;148:705.*
- *Nolan S, Scoggin JA. Serotonin syndrome: recognition and management. U.S. Pharmacist. 2002. Available at: www.uspharmacist.com/oldformat.asp?*

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